MEDICAL POLICY	Genetic Testing: CADASIL Disease
Effective Date: 12/1/2021  12/1/2021 Medical Officer Date	Medical Policy Number: 238 Medical Policy Committee Approved Date: 12/17; 12/18; 6/19; 8/2020; 08/2021; 09/2021

See Policy CPT section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- Clinical notes to include the following:
  - Documentation of genetic counseling as required in the policy criteria below which includes how test results will impact clinical decision making
  - Reason (indication) for performing test, including the suspected condition
  - Existing signs and/or symptoms related to reason for current test request
  - Prior test/laboratory results related to reason for current test request
  - Family history, if applicable
  - How results from current test request will impact clinical decision making

- All relevant CPT/HCPCS codes billed

POLICY CRITERIA

Genetic Testing: Symptomatic Individuals

All Lines of Business

I. Genetic testing for *NOTCH3* variants may be considered **medically necessary and covered** to confirm the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in a symptomatic individual when **all** of the following (A.-E.) criteria are met:

   A. Genetic Counseling general criteria have been met; **and**
   B. The patient has a family history of stroke and/or vascular dementia; **and**
   C. Documented presence of white matter hyperintensity lesions in the brain by neuroimaging; **and**
   D. The patient is experiencing **at least one** of the following (1.-4.) clinical signs:
      1. Subcortical ischemic events; **and/or**
      2. Cognitive impairment; **and/or**
      3. Migraine with aura; **and/or**
      4. Psychiatric disturbances (e.g., mood disturbances; apathy); **and**
   E. Alternate methods of testing for CADASIL have failed to establish a diagnosis (e.g., skin biopsy).

II. Genetic testing for CADASIL is considered **investigational and not covered** in all other situations, including but not limited to when criteria I. above are not met, or when testing for genes other than *NOTCH3*.

Genetic Testing: Asymptomatic Individuals

All Lines of Business Except Medicare

III. Genetic testing for *NOTCH3* variants in asymptomatic adults (18 years of age or older) may be considered **medically necessary and covered** when both of the following are met:

   A. Genetic Counseling general criteria have been met; **and**
   B. A first- or second-degree adult relative* has documented confirmation of a *NOTCH3* pathogenic variant **and** a confirmed diagnosis of CADASIL. (See Policy Guidelines below)

IV. Genetic testing for CADASIL is considered **not medically necessary and not covered** in asymptomatic individuals if they are under the age of 18 years.

Medicare Only

V. Genetic testing of at-risk asymptomatic individuals is considered **not medically necessary and is not covered**. Such testing is considered screening and is excluded by Medicare statute.

Link to Policy Summary

POLICY GUIDELINES

*First-degree relatives are parents, siblings, and children. Second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings (siblings with one shared biological parent).

Although CADASIL is inherited in an autosomal dominant manner, clinical presentation can vary within a family. As a result, affected members within a family may be misdiagnosed or underdiagnosed due to late-onset and variability in clinical presentation. Therefore, an extended family pedigree should be assessed and confirmation of a CADASIL diagnosis in either a first- or second-degree relative is indicated.[1]

CPT CODES

All Lines of Business Except Medicare	
Prior Authorization Required	
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) – when used for "Notch 3 (NOTCH3) targeted sequence analysis. Notch 3 (NOTCH3) targeted sequence analysis of exons 1-23."

DESCRIPTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare, inherited brain disorder that causes mid-adult onset migraine headaches and multiple, recurrent ischemic strokes. The prevalence is thought to be between 2-4/100,000. Although CADASIL is considered an adult-onset disease, with the mean age of onset typically in the third or fourth decade of life, symptoms such as migraine with aura have been documented in patients as early as six years of age.[2,3]

CADASIL is inherited in an autosomal dominant manner.[4] However, a family history consistent with autosomal dominant inheritance supports the diagnosis but is not required, as affected family members may have been misdiagnosed due to varying clinical presentation within families and inaccurate reporting of negative family history. In addition, clinical presentation of the disease varies within and between families. More than 95% of individuals with CADASIL have pathogenic mutations in the *NOTCH3* gene on chromosome 19 and *de novo* pathogenic mutations appear to be rare.[1]

The pathologic hallmarks of CADASIL are electron-dense granules in the media of arterioles as detected by electron microscopy, and increased expression of the Notch3 protein in the arterial wall detected by

immunostaining, both which can be evaluated in a skin biopsy. The combined analysis by electron microscopy and immunohistochemistry, when interpreted by an experienced neuropathologist, usually allows for a conclusive CADASIL diagnosis. However, the sensitivity of the electron microscopy is variable. Of note, there are currently no generally accepted diagnostic criteria for CADASIL.[1]

Brain imaging abnormalities are also common signs of CADASIL, which may be detected in asymptomatic and symptomatic individuals. These abnormalities evolve as the disease progresses. Characteristic abnormalities can be detected by MRI as early as the 20s, but are not considered to be diagnostic.[5]

REVIEW OF EVIDENCE

Since the analytical and clinical validity of testing for *NOTCH3* pathogenic variants for the diagnosis of CADASIL have been established, the evidence review below will focus on the clinical utility of testing. In the present context, clinical utility was evaluated in the following situations:[6]

- Confirmation of a diagnosis in a symptomatic individual
- Identification of asymptomatic at-risk family members

Confirmation of a CADASIL Diagnosis in a Symptomatic Individual

No studies were identified that reported on how confirmation of a CADASIL diagnosis by way of a positive result for NOTCH3 mutation testing led to changes in medical management or improved outcomes for symptomatic patients. However, the value of genetic testing for NOTCH3 diagnostic variant effectually ends the diagnostic odyssey for these patients and prevents patients from having to undergo further testing.

Recently, groups in Japan and Italy published updated diagnostic criteria based on evaluation of the frequencies of clinical features in large case/control studies that included patients with genetically confirmed CADASIL.

In 2017, Mizuta et al. reported that the presence of white matter lesions was the feature given the strongest weight in the new criteria, based on the frequency among 102 CADASIL confirmed Japanese patients.[7] In this study, a definite diagnosis included a positive NOTCH3 result, presence of white matter lesions, and exclusion of leukodystrophy.

In 2018, Bersano et al. recruited 128 patients to evaluate clinical and neuroimaging features important in the diagnosis of CADASIL.[8] This study found that a family history of stroke, the presence of dementia and external capsule lesions on MRI were the only features significantly associated with the diagnosis of CADASIL. Both of these recent studies reported that using updated criteria including presence of specific lesions in the brain and a more flexible requirement for family history increased the yield for genetic testing.

Identification of Asymptomatic At-Risk Family Members

In 2012, Reyes et al. published the results of a study that investigated the characteristics, motivations and long-term outcome of testing of asymptomatic subjects at risk of CADASIL.[9] This series on genetic

screening examined sociodemographic, motivational, and psychological variables of health individuals at risk for CADASIL who enrolled over a seven-year period. Although only 33 subjects requested genetic testing for CADASIL risk, the authors reported a high dropout rate (63% after the initial assessment). Of the 11 subjects who the six-month study period, six were carriers of the mutation and were still asymptomatic after a mean follow-up of 19 months. No negative events were reported; all reported a high overall quality of life, and two carriers gave birth to their first child. Although a very small sample, this study provided some evidence of clinical utility of presymptomatic genetic testing for CADASIL and suggests that resulting knowledge of risk for this disorder does not produce detrimental effects on overall quality of life.

CLINICAL PRACTICE GUIDELINES

American College of Radiology (ACR)

The 2015 ACR evidence-based appropriateness criteria on dementia and movement disorders have no imaging recommendations at this time for CADASIL. The ACR panel stated that certain structural MRI changes in these patients may help to suggest the diagnosis, but, "diagnosis is confirmed by skin biopsy or detection of a pathogenic NOTCH3 mutation on direct sequencing."[10]

European Federation of Neurological Sciences (EFNS)

Although not U.S. based, in 2010, the EFNS completed a well-conducted, evidence-based guideline on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementia.[11] The guideline a high recommendation for direct sequencing of exons 3 and 4 as a first step if clinical suspicion of CADASIL. The guideline also stated, "the diagnosis may *also be supported* by skin biopsy showing typical osmiophilic granula" by electron microscopy. [11] This recommendation was given a Level B rating, indicating that the genetic testing as being, "probably useful/predictive" and was based on evidence comprised of, "at least one convincing class II study or overwhelming class III evidence".

CENTERS FOR MEDICARE & MEDICAID

As of 07/25/2021, no Centers for Medicare & Medicaid (CMS) coverage guidance was identified which addresses *NOTCH3* testing for the diagnosis of CADASIL in symptomatic individuals.

CMS Guidance on Genetic Screening Tests

According to the Medicare Claims Processing Manual, Chapter 16: Section 120.1[12]

> "Tests that are performed in the absence of signs, symptoms, complaints, personal history of disease, or injury are **not covered** except when there is a statutory provision that explicitly covers tests for screening as described.
>
> If a person is tested to rule out or to confirm a suspected diagnosis because the patient has a sign and/or symptoms, this is considered a diagnostic test, not a screening test. A/B MACs (A) and (B) have discretionary authority to make reasonable and necessary scope of benefit determinations."

POLICY SUMMARY

Despite insufficient evidence of clinical utility for the genetic testing of NOTCH3 for CADASIL, testing for pathogenic mutations can help diagnose CADASIL in patients when other tests have yielded inconclusive results, thereby ending the diagnostic odyssey. Despite the fact the CADASIL is considered an adult-onset disease, testing in this situation is appropriate for patients of all ages, children under the age of 18 years may present with symptoms. Lastly, genetic testing of NOTCH3 to confirm a diagnosis of CADASIL in this situation is supported by current clinical practice guidelines.

Despite insufficient evidence of clinical utility for the genetic testing of NOTCH3 for CADASIL, testing for NOTCH3 mutations in at-risk adults with a family history of CADASIL and a known pathogenic mutation can help individuals make reproductive planning decisions and avoid unnecessary diagnostic testing.

Genetic testing for CADASIL is considered not medically necessary and not covered in asymptomatic individuals if they are under the age of 18 years. Testing of asymptomatic children for adult-onset disorders is recommended against by major medical associations.

There is insufficient evidence that genetic testing for CADASIL alters decision-making or directs management in individuals that do not meet the medical necessity criteria outlined above. In addition, there is a lack of support from clinical practice guidelines for genetic testing for CADASIL in populations other than symptomatic patients that meet the medical necessity criteria outlined above.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days' notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

MEDICAL POLICY CROSS REFERENCES

- Genetic Counseling
- Genetic Testing: Reproductive Planning and Prenatal Testing (All Lines of Business Except Medicare)
- Genetic Testing: Reproductive Planning and Prenatal Testing (Medicare Only)

REFERENCES

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